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Food and Drug Administration

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Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Monograph for Over-the-Counter Bronchodilator Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; withdrawal of previous proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph (FM) for over-the-counter (OTC) bronchodilator drug products to add additional warnings (e.g., an “Asthma alert”) and to revise the indications, warnings, and directions in the labeling of products containing the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, epinephrine, epinephrine bitartrate, racephedrine hydrochloride, and racepinephrine hydrochloride. This proposed rule is part of FDA’s ongoing review of OTC drug products. FDA is also withdrawing the proposed rule (see the **Federal Register** of July 27, 1995 (60 FR 38643)) to remove the ephedrine ingredients from the FM.

DATES: Submit written or electronic comments on the proposed monograph amendment and on FDA’s economic impact determinations by [*insert date 120 days after date of publication in the **Federal Register***]. The date of withdrawal of the July 27, 1995, proposed rule is [*insert date of publication in the **Federal***

Register]. Please see section XI of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1995N-0205 and/or RIN number 0910-AF32, by any of the following methods:

- Federal eRulemaking Portal: *<http://www.regulations.gov>*. Follow the instructions for submitting comments.
- Agency Web site: *<http://www.fda.gov/dockets/ecomments>*. Follow instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 1995N-0205 and/or RIN number 0910-AF32 in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions):
Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. or Regulatory Information Number (RIN) for this rulemaking. All comments received will be posted without change to *<http://www.fda.gov/ohrms/dockets/default.htm>*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *<http://www.fda.gov/ohrms/dockets/default.htm>* and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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I. Background

A. Advance Notice of Proposed Rulemaking (ANPRM)

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an ANPRM to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The Panel recommended that ephedrine and epinephrine preparations be category I (generally recognized as safe and effective) for OTC bronchodilator use (41 FR 38312 at 38370 through 38372).

B. Tentative Final Monograph (TFM) and FM

FDA concurred with the Panel in the bronchodilator TFM (47 FR 47520 at 47527, October 26, 1982). FDA included the following active ingredients in the FM for OTC bronchodilator drug products: Ephedrine ingredients (ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride) and epinephrine ingredients (epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride) (51 FR 35326 at 35339, October 2, 1986). In this current proposed rule, the term “ephedrine ingredients”

includes the four active ingredients included in the FM; the term “epinephrine ingredients” includes the three active ingredients included in the FM; and the term “OTC bronchodilator drug products” includes products containing any of these seven active ingredients.

C. Proposal to Remove Ephedrine Ingredients From the OTC Bronchodilator FM

In the **Federal Register** of July 27, 1995 (60 FR 38643), FDA published a proposed rule (the 1995 proposal) to amend the FM for OTC bronchodilator drug products. It proposed to remove the ephedrine ingredients (ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride) and to classify those ingredients as not generally recognized as safe and effective for OTC use. At that time, FDA reassessed the benefit/risk of OTC ephedrine drug products and proposed their removal because of safety concerns, including the potential for these products to cause harm as a result of misuse and abuse. Interested persons were invited to submit written comments or objections to the 1995 proposal and FDA’s economic impact determination by August 28, 1995.

II. Comments Received in Response to the 1995 Proposal to Remove Ephedrine Ingredients From the OTC Bronchodilator FM

A. Number of Comments Received

FDA received comments from 56 consumers, 37 health professionals, 8 manufacturers of OTC bronchodilator drug products, 5 Federal and State government agencies, 5 national associations, 4 boards of pharmacy, 2 distributors of dietary supplements, 1 consulting firm, and 1 member of Congress. Several comments addressed FDA’s economic impact determination. Copies of the comments and additional information that have come to FDA’s

attention since publication of the 1995 proposal are on public display in the Division of Dockets Management (see **ADDRESSES**).

B. Summary of Comments Received

(Comment 1) Several comments contended that the 1995 proposal does not indicate whether FDA had analyzed whether additional labeling warnings (including restrictions on distribution) would address FDA's concerns about safer OTC use of ephedrine drug products, especially by young people. The comments stated that FDA should use its authority to amend current product labeling warnings required by the FM for OTC bronchodilator drug products.

(Comment 2) The comments suggested a number of reasons for the potential unsafe use of OTC ephedrine drug products:

- Virtually all of the unsafe use is related to products with brand names that promote the unapproved pharmacological effects of ephedrine.
- Although these products are labeled with the required FDA bronchodilator labeling, they are promoted in the marketplace as stimulants, weight loss products, and performance enhancers.
- These products are readily available for sale in convenience stores, service stations, and truck stops or by magazine mail order.
- Little or no restrictions exist on the sale of these products to teenagers and children.
- FDA and the Federal Trade Commission have not utilized their enforcement authority to address the safety problems associated with improper promotion of these products, which is the main problem.

(Comment 3) Several comments made suggestions concerning OTC sales of these products. These included the following recommendations:

- Proof of age should be required to reduce purchase of these products by children.

- Ephedrine and its salts should be placed under schedule V of the Controlled Substances Act to control sales, while allowing people who have a legitimate medical need for the products to purchase them.

- States could restrict OTC sale of ephedrine drug products.

(Comment 4) Many comments supported FDA's proposal to remove ephedrine active ingredients from the OTC marketplace. In addition, these comments presented the following arguments against the sale of all OTC bronchodilator drug products:

- Easy access leads to self diagnosis, results in the delay of treatment, and may mask other symptoms.

- People who use OTC bronchodilators do not receive patient education about their disease, about the medication, or about the product's possible side effects on the heart and central nervous system.

- OTC availability allows the products to be sold to individuals of any age and implies that mild asthma is not serious, despite the fact that people with mild asthma can die from the disease.

- People can make deadly mistakes if they do not use these products properly.

- People do not, or cannot, read the product's warnings and do not always understand or heed what they read.

- Parents often use these products for their small children, even though interaction with a pediatrician is necessary for treating a child's asthma.

- OTC bronchodilators are often used for unintended purposes.

(Comment 5) Several comments cited a number of problems occurring in their States as a result of the unrestricted availability of OTC ephedrine drug

products. These included the use of higher than the labeled doses, prolonged use of products, use for unapproved indications (e.g., for weight loss and as a stimulant), and improper use, particularly by children.

(Comment 6) A few comments addressed the OTC availability of epinephrine aerosol dosage forms¹ and dietary supplements that contain ephedrine alkaloids or ephedra.²

III. FDA's Response to the Comments

After considering the comments submitted for the 1995 proposal to remove ephedrine and other active ingredients from the FM, FDA is withdrawing that proposal. The scope and coverage of this current proposed rule differ from the 1995 proposal. FDA has given serious consideration to the various arguments presented by the comments on the 1995 proposal, has considered other information, and has determined that ephedrine and other bronchodilator ingredients should remain in the FM for self-treatment of mild bronchial asthma for several reasons:

- There are people with diagnosed mild bronchial asthma for whom the benefits of symptomatic treatment with OTC bronchodilators for temporary wheezing, shortness of breath, and tightness of chest outweigh the risks of use.

¹ The 1995 proposal did not involve epinephrine aerosol dosage forms. In the **Federal Register** of May 20, 1996 (61 FR 25142), FDA amended the bronchodilator drug products FM by removing pressurized metered-dose aerosol container dosage forms for the ingredients epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride. The bronchodilator FM currently includes these three epinephrine ingredients only for use in a hand-held rubber bulb nebulizer (21 CFR 341.76(d)(2)). Accordingly, because these ingredients in pressurized metered-dose aerosol container dosage forms are not included in this document, FDA is not addressing the comments on this dosage form.

² The 1995 proposal on OTC bronchodilator drug products did not involve dietary supplements. FDA has addressed dietary supplements containing ephedrine alkaloids separately in a final rule that published on February 11, 2004 (69 FR 6788), under Docket No. 1995N-0304. The final rule declared dietary supplements containing ephedrine alkaloids adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 342(f)(1)(A)) because they present an unreasonable risk of illness or injury. Accordingly, dietary supplements containing ephedrine alkaloids may no longer be marketed in the United States.

- Additional labeling warnings and directions in this current proposal provide information to promote safer use of these products.
- FDA has taken regulatory action against ephedrine drug products with misleading brand names that promoted weight loss, enhancement of athletic performance, or stimulant uses.
- Drug Enforcement Administration (DEA) requirements restricting the sale of ephedrine, its salts, optical isomers, and salts of optical isomers that became effective after FDA published the 1995 proposal are in effect and, among other things, require single-ingredient ephedrine drug products to be sold behind the counter. Therefore, access to these products is controlled.

A. Asthma and Its Treatment With Ephedrine

Asthma is a chronic lung disease caused by inflammation of the airways, resulting in episodes of airway narrowing and obstruction. Asthma can be serious and should be diagnosed and treated by a physician. Although there is no cure for asthma, appropriate management most often leads to control of the condition. FDA notes that the Panel stated that sympathomimetic drugs (e.g., ephedrine) are used to overcome the spasm that causes narrowing of the bronchial air tubes, and the usefulness of ephedrine is limited to the milder forms of asthma (41 FR 38312 at 38370 through 38371).

In assessing ephedrine, the Panel relied on data from two studies conducted in 1973 and 1975, respectively. The patient population enrolled in these studies was not only clinically stable (i.e., normal electrocardiogram, blood pressure, and pulse), but also had no apparent history of adverse events related to treatment with other stimulant bronchodilators used at the time. One study was a double-blind comparison of 24 milligrams (mg) ephedrine and a combination of 24 mg of ephedrine and 130 mg theophylline (41 FR 38312

at 38371). Measurements including specific airway resistance, vital capacity, and forced expiratory volume in 1 second (FEV₁) showed that ephedrine significantly decreased the airway resistance and increased both capacity and FEV₁ over a 2-hour period. This effect was enhanced and prolonged by the presence of theophylline, a prescription drug. The Panel cited another study comparing ephedrine and terbutaline (a prescription drug) in 26 asthmatics. The data indicated that 25 mg ephedrine resulted in significant improvement in the pulmonary function tests between 120 and 240 minutes after taking a single dose (41 FR 38312 at 38371). The results were similar to 2.5 mg terbutaline, but less than the effect of 5 mg terbutaline. These clinical studies supported improvement in pulmonary function tests between 2 and 4 hours after taking a single dose of 25 mg ephedrine, with the improvements lasting up to 4 hours. These studies support the use of ephedrine for patients with asthma who are otherwise clinically stable (i.e., not found by a physician to have high blood pressure or other cardiovascular risk).

Ephedrine is an α and β adrenergic agonist and also enhances the release of norepinephrine from sympathetic neurons. In addition to its bronchodilation effect, other effects of ephedrine are related to its pharmacodynamic actions through α and β adrenergic receptors (Ref. 1). These include awareness of heart beat, rapid heart beat, and variable increases of blood pressure. The Panel indicated that a study by Dulfano and Glass on 26 asthmatics between 28 and 61 years old showed that (at measured intervals of 15, 30, 60, 120, 180, and 240 minutes) a single dose of 25 mg ephedrine had no significant effect on either heart rate or blood pressure (41 FR 38312 at 38370).³ The Panel also

³ The authors reported maximal cardiovascular effects at 180 minutes after administration of ephedrine compared to control (baseline): Heart rate (beats per minute) decreased from 91.6 to 83.1; blood pressure (millimeters of mercury (mm Hg)), systolic increased from 127.8 to 129.9 and diastolic increased from 81.0 to 82.4.

cited a study by Tashkin and Simmons of the cardiovascular effects of 25 mg ephedrine (over a 7-hour period) in 20 asthmatics. The Panel noted that there was only a modest increase in heart rate of up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change (41 FR 38312 at 38370).⁴

In 1988, Chua and Benrimoj reviewed the blood pressure effects of OTC sympathomimetic drugs, including ephedrine (Ref. 2). They made the following observations:

- McLaurin et al. (1961) and Laitinen et al. (1982) found 25 mg of ephedrine produced no significant effect on blood pressure and heart rate of normotensive patients.
- Tashkin et al. (1975) obtained similar results when comparing the cardiovascular and bronchial effects of terbutaline with ephedrine.
- Bye et al. (1974) demonstrated a significant rise in systolic blood pressure of 17 and 7 millimeters of mercury (mm Hg) with 50 and 25 mg of ephedrine, respectively, but no effect on diastolic blood pressure.
- Elis et al. (1967) showed that a single oral dose of 30 mg ephedrine produced an average increase in mean arterial blood pressure of 5 mm Hg.
- Drew et al. (1978) showed that oral doses of 60 mg ephedrine produced significant increases in systolic and diastolic blood pressure in normotensive subjects.
- The discrepancy between Bye et al. and McLaurin et al. may be due to the different parameters analyzed and the time intervals for blood pressure measurement.

⁴ The authors reported that after ephedrine, mean heart rate was significantly higher than control (baseline) values (average 7.4 to 10.9 beats per minute) at 2 to 5 hours as well as mean placebo values (average 7.7 to 10.6 beats per minute at 2, 4, and 5 hours). The authors measured blood pressure over a 7-hour period after the subjects took ephedrine.

Other information also supports a pressor effect (increases blood pressure) of ephedrine. Intravenous ephedrine is used to increase blood pressure in patients with hypotension during spinal and epidural anesthesia, particularly during obstetrical procedures (Ref. 3).

In the recent final rule on dietary supplements containing ephedrine alkaloids (69 FR 6788, February 11, 2004), FDA discussed the results from a study by Boozer et al. (Ref. 4). That study evaluated the blood pressure effects of a combination of ephedrine alkaloids and caffeine compared to placebo over a 6-month period. Using automated blood pressure measurements over 24 hours at weeks 1, 2, and 4, the ephedrine alkaloid and caffeine group had significantly higher blood pressure measurements after 4 weeks of treatment. The effect reported in this study cannot be attributed to the caffeine because the effect of caffeine on blood pressure is transient, and the acute effect of caffeine to increase blood pressure is lost within 2 weeks of continued use (69 FR 6788 at 6802). FDA finds that the collective evidence suggests that ephedrine at doses recommended for a bronchodilator effect causes elevation of blood pressure. Some individuals who use ephedrine are at risk of experiencing adverse effects from therapy because of ephedrine's effect on blood pressure. Despite the results of the Boozer study and other evidence, FDA considers the therapeutic benefits of ephedrine as an OTC bronchodilator outweigh its effects in elevating blood pressure based on its temporary and intermittent use. (See also section III.B of this document.)

According to the National Asthma Education and Prevention Program guidelines, mild intermittent asthma is defined as having symptoms no more than twice a week during the day or twice a month at night (Ref. 5). Between asthmatic episodes, these asthmatics have no symptoms and can maintain a

normal level of activity. FDA has determined that people with mild intermittent asthma are the only category of asthmatics who should be candidates for oral ephedrine. Asthmatics with more severe asthma disease (i.e., persistent asthma) should be under the care of a physician for consideration of additional therapy to control the disease (Ref. 6).

The Panel noted that wide use of epinephrine aerosols for temporary relief of milder forms of asthma has been attended by few and mild side effects. The Panel cited a double-blind study in asthmatics during which epinephrine aerosol demonstrated a significant increase in bronchial air flow in 15 minutes accompanied by symptomatic relief, whereas the placebo gave little change (41 FR 38312 at 38372). The Panel concluded that epinephrine is a safe and effective OTC bronchodilator ingredient when used according to recommended labeling, and FDA included epinephrine in the FM (51 FR 35326 at 35332 through 35333).

B. Benefit-Risk Assessment

FDA has done a benefit-risk assessment of the different uses of ephedrine ingredients. FDA has determined, based on its review of the available information, that the benefits of single-dose ephedrine ingredients for the temporary relief of mild asthma outweigh the risks. In contrast, FDA determined for dietary supplements containing ephedrine alkaloids that the risks of use outweigh any benefits.

In the **Federal Register** of February 11, 2004, FDA declared dietary supplements containing ephedrine alkaloids adulterated under the act because they present an unreasonable risk of illness or injury based on a risk-benefit analysis (69 FR 6788 at 6824). After reviewing the available data on weight loss, enhancement of athletic performance, eased breathing in healthy

individuals, and other uses, FDA concluded that the data do not indicate that these dietary supplement products containing ephedrine alkaloids provide a benefit sufficient to outweigh the risks. FDA stated that there is sufficient evidence to conclude that ephedrine alkaloids can increase blood pressure and heart rate. FDA also stated that dietary supplements containing ephedrine alkaloids “expose users to several risks, including the consequences of a sustained increase in blood pressure (e.g., serious illnesses or injuries that include stroke and heart attack that can result in death) and increased morbidity and mortality from worsened heart failure and proarrhythmic effects” (69 FR 6788 at 6827). FDA also stated that although the proarrhythmic effects of dietary supplements containing ephedrine alkaloids typically occur only in susceptible individuals, the long-term risks from elevated blood pressure can occur even in nonsusceptible, healthy individuals (69 FR 6788 at 6827). FDA concluded that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. FDA does not consider its decision on the use of ephedrine alkaloids in dietary supplements as precluding the use of sympathomimetic ingredients in other regulated products for appropriate populations. The benefits compared to risks should be analyzed in each instance.

In the clinical studies discussed in section III.A of this document, ephedrine demonstrated a bronchodilator effect in subjects with mild asthma. This bronchodilator effect provides temporary relief of shortness of breath, tightness of the chest, and wheezing due to bronchial asthma. These OTC

ephedrine drug products provide health benefits when used by appropriate populations (i.e., mild asthmatics) for a limited period of time by relieving the symptoms of an asthma attack and possibly reducing symptom progression. Relieving symptoms of a mild asthma attack is an important benefit. The relief of symptoms enables an asthmatic to perform normal everyday activities without restrictions brought on by shortness of breath. The finding that OTC single-ingredient ephedrine drug products provide a health benefit for mild asthmatics justifies the continued marketing of such products despite the risks. This favorable benefit-risk assessment distinguishes ephedrine as a drug from FDA's unfavorable benefit-risk assessment for dietary supplements containing ephedrine alkaloids.

FDA's decision in this proposed rule to have a different position for OTC drug products that contain ephedrine compared to dietary supplements that contain ephedrine alkaloids is not arbitrary or capricious. The decision is based on differences in the intended uses of these products, as well as differences in the scientific evidence available to support the risk-benefit ratio for the products. The risk-benefit ratio is dependent on several factors, including the product's intended use, the product's benefits, if any, and the availability of adequate measures to control risk.

FDA recognizes the risks associated with ephedrine containing drug products. However, there are several differences between OTC drug products containing ephedrine and dietary supplements that contain ephedrine alkaloids that may be relevant to the differing risk-benefit profiles of these products.

- Ephedrine used in a drug product in the treatment of asthma needs to meet the United States Pharmacopeia (USP) standards of identity, strength,

quality, and purity. The USP ingredients contain not less than 98 or 98.5 percent and not more than 100.5 or 101 percent of the declared amount of ephedrine, ephedrine hydrochloride, or ephedrine sulfate (Ref. 7). The botanical sources of ephedrine that were used in dietary supplement products did not have to meet USP standards and contained varying amounts of ephedrine and other ephedrine alkaloids depending upon the botanical species that were used. Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially, ephedrine was typically the predominant alkaloid in the raw material (69 FR 6788 at 6789).

- Botanical sources of ephedrine alkaloids contain ephedrine and other sympathomimetics, including norephedrine, pseudoephedrine, and methylephedrine. All of these compounds are pharmacologically active and have variable effects on adrenergic receptors. These variable effects depend on several factors including dosages, route of administration, and individual susceptibility (Ref. 8). For example, in the Hemorrhagic Stroke Project Study, the use of phenylpropanolamine (a sympathomimetic drug) was associated with a statistically significant increased risk for hemorrhagic stroke (Ref. 9) whereas pseudoephedrine was not (Ref. 10). The combination of sympathomimetic compounds may have additional pharmacological effects on the cardiovascular system compared to ephedrine alone and, as a consequence, may have additive risks.

- In previous **Federal Register** notices (47 FR 35344, August 13, 1982; 48 FR 52513, November 18, 1983; and 49 FR 26814, June 29, 1984), FDA recognized the negative consequences of combining multiple sympathomimetic ingredients or a sympathomimetic plus caffeine in the same drug product. In

these notices, FDA defined any drug product containing ephedrine in combination with phenylpropanolamine or caffeine as a new drug requiring a new drug application for marketing. At the time, FDA was concerned about the additive effects of the combination of two or more sympathomimetic ingredients without any demonstrated enhanced benefit. FDA has not permitted marketing of OTC drug products containing more than one sympathomimetic drug because of safety concerns.

FDA has received and evaluated adverse reaction reports on both drug products containing ephedrine and dietary supplements containing ephedrine alkaloids. Based on the differences in composition described in the previous paragraphs between the drug products and dietary supplements, adverse event data for dietary supplements containing ephedrine alkaloids may not be completely applicable to OTC ephedrine drug products.

FDA acknowledges that OTC drug products containing ephedrine ingredients may be used by consumers who are obese or have high blood pressure and that these products can cause adverse events. Because sympathomimetic ingredients may pose risks for adverse events, even after a single dose, FDA has considered the benefits and risks associated with the use of these products by these consumers. While OTC ephedrine drug products are not without risk, they have demonstrated benefit for asthmatics in the intermittent and temporary treatment of the symptoms associated with mild asthma. FDA concludes that the benefit from lessening the severity of an asthma attack outweighs the risk of an increase in blood pressure when OTC ephedrine drug products are taken in accordance with a warning to ask a doctor before use if you have heart disease or high blood pressure and with the recommended dosage.

After reviewing the safety and effectiveness information on ephedrine in OTC drug products, FDA has determined that the benefits of OTC drug products containing single ingredient ephedrine outweigh the risk when the product is used according to labeled instructions. In determining that the benefit outweighs the risk for the marketing of ephedrine in OTC drug products, FDA finds that there continues to be a clinically meaningful benefit derived by asthmatics using these products on an intermittent basis for the temporary relief of bronchospasm. FDA continues to believe that OTC drug products containing single ingredient ephedrine are generally recognized as safe and effective and are not misbranded under the conditions of use in the bronchodilator FM and with the labeling in this proposed rule.

C. Labeling for OTC Bronchodilator Drug Products

Product labeling (indications, warnings, and directions) is important for the safe and effective use of ephedrine OTC drug products. The current and new proposed labeling instructs asthmatics how to use the product correctly in order to minimize risks. Labeling recommends use only for the intermittent treatment of mild symptoms of asthma. Labeling also alerts certain populations with conditions that increase the risk of adverse events to seek advice from a health care provider before using the product. Any deviation from the labeling may put an asthmatic at increased risk for an adverse event and prevent maximum benefit from the drug. For example, if an asthmatic uses an OTC ephedrine drug product on a daily basis over a prolonged period of time because of recurrent symptoms, there are increased risks associated with the long-term use of ephedrine and with inadequate treatment of the asthma condition. The indications, warnings, and directions (including dosage directions) define the conditions of use of the ingredient. If the drug is not

used as labeled, the risks may outweigh the benefits of the drug. The proposed new labeling for OTC bronchodilator drug products is intended to inform asthmatics about the safe and effective use of these drug products. The labeling is also intended to inform asthmatics that if their asthma condition worsens, with more frequent or more severe symptoms, they should immediately consult a physician to reassess the management of the asthmatic condition and to consider an alternative drug therapy.

FDA stated in the dietary supplement rule that warning statements cannot adequately protect consumers from the risks associated with dietary supplements containing ephedrine alkaloids (69 FR 6788 at 6828). In this proposed rule, FDA is proposing new warning statements and labeling to minimize the risks associated with taking OTC drug products containing ephedrine ingredients. The difference is based on the favorable benefit-risk ratio associated with the OTC drug products containing ephedrine ingredients for the treatment of mild asthma. Unlike dietary supplements, OTC drug products have demonstrated benefits in the treatment and mitigation of disease. Based on controlled clinical investigations (see § 330.10(a)(4)(ii)), FDA determined that the benefits associated with the use of OTC drug products containing ephedrine for disease indications outweigh the risks and justify the use of these products despite their risks. However, such uses for disease mitigation and treatment are beyond the scope of permissible dietary supplement uses (69 FR 6788 at 6810). FDA considers the OTC drug products containing ephedrine ingredients to be safe and effective and not misbranded for the treatment of physician-diagnosed mild cases of asthma when appropriately labeled, including appropriate warning statements. The FM contains labeling that advises a user of these products:

- Not to use this drug unless a diagnosis of asthma has been made by a doctor,
- Not to use the drug if you have certain medical conditions, and
- To consult a doctor when the drug does not provide relief within a specific time interval or causes side effects that persist.

FDA continues to consider the two types of currently marketed OTC bronchodilator sympathomimetic ingredients, ephedrine and epinephrine, to be safe and effective for the self-treatment of mild asthma. These ingredients have slightly different actions. Oral ephedrine provides less bronchial muscle relaxation but has a more sustained effect than inhaled epinephrine. FDA recognizes that use of OTC epinephrine aerosol drug products to relieve the symptoms of mild asthma may elicit sympathomimetic effects similar to those elicited by oral ephedrine ingredients. Consequently, because of the pharmacological similarities of these two sympathomimetic active ingredients, FDA considers similar labeling of OTC ephedrine and epinephrine drug products necessary to inform consumers of the safe and effective use of these OTC drug products. As previously stated, FDA continues to believe that people with mild asthma can properly use OTC bronchodilator drug products to self-treat occasional wheezing, shortness of breath, and tightness of chest after their asthma has been diagnosed by a physician. FDA has determined, however, that to help ensure safe and effective use and to minimize the risks of OTC bronchodilator drug products, additional labeling is needed for these products.

1. Uses

The current indications for OTC bronchodilator use are in § 341.76(b)(1) and (b)(2). The primary indication is “For temporary relief of shortness of

breath, tightness of chest, and wheezing due to bronchial asthma”

(§ 341.76(b)(1)).

The labeling of the product may also state one or both of the following uses (§ 341.76(b)(2)):

- “For the” (select one of the following: “temporary relief” or “symptomatic control”) “of bronchial asthma.”
- “Eases breathing for asthma patients” (which may be followed by: “by reducing spasms of bronchial muscles”).

Two of these indication statements mention temporary relief, while the third statement does not. Also, in the second statement manufacturers have the option of selecting either “temporary relief” or “symptomatic control.” For safe and appropriate use, these use statements should inform consumers that these products are to be used for temporary relief of occasional symptoms of mild asthma. Therefore, FDA is proposing to revise the indication statement in § 341.76(b) to a single statement as follows: “for temporary relief of occasional symptoms of mild asthma: [bullet] wheezing [bullet] tightness of chest [bullet] shortness of breath”.

2. Warnings

a. *Warnings related to effects on the cardiovascular system.* Oral ephedrine has effects on the cardiovascular system (Refs. 11 through 14). Cardiovascular effects include elevation of the systolic and diastolic blood pressure (Ref. 11). Other effects include awareness of heartbeat and rapid heartbeat accompanied usually by some elevation of blood pressure (Ref. 14). Pressor responses are due partly to vasoconstriction but mainly to cardiac stimulation. The force of myocardial contraction is enhanced by the drug, and cardiac output is augmented, provided venous return is adequate. The renal, abdominal, and

intestinal blood flows are decreased; whereas the coronary, cerebral, and muscle blood flows are increased (Ref. 11).

FDA is aware of reported adverse drug events on the cardiovascular system associated with the use of ephedrine-containing drug products. Similar events have been reported for dietary supplement products containing ephedrine alkaloids (69 FR 6788 at 6814 through 6815). The reported adverse events include elevations in blood pressure and/or heart beat, and serious adverse events include abnormal heart rhythm (arrhythmias), heart attack, and stroke. These adverse events are consistent with the known pharmacology of sympathomimetic drugs, as reported in the literature. The reports we have received for ephedrine containing bronchodilator drug products were associated with use that was more frequent or in higher amounts than the labeled dose. However, even at recommended doses, many people have an increased risk for a serious side effect to occur.

Sympathomimetic drugs, including ephedrine ingredients, mimic the effects (stimulation of the sympathetic nervous system) of naturally occurring epinephrine and norepinephrine (Ref. 11). In addition to their direct pharmacological effects, many of these ingredients also stimulate the release of norepinephrine from nerve endings. The release of norepinephrine further increases the sympathomimetic effects of these drugs on the body, at least transiently. Susceptible individuals, who have coronary artery disease or heart failure and use sympathomimetic drugs, are at increased risk for serious adverse events, including heart attack, stroke, and death. Sympathomimetic drugs also can cause abnormal heart rhythms (pro-arrhythmic effect) and can induce cardiac arrhythmias in susceptible individuals, such as those with

underlying coronary artery disease, heart failure, or an abnormal cardiac conduction system.

Over longer periods of use, the risk for adverse health effects to susceptible individuals becomes greater due to a sustained elevation in blood pressure. Ephedrine and epinephrine ingredients are expected to, and evidence indicates that they do, have similar pharmacological effects, such as increased blood pressure and heart rate, to those of other sympathomimetic ingredients (Refs. 11 and 12). The pharmacological effects of ephedrine and epinephrine (and other sympathomimetics), both efficacious and adverse, will vary dependent of the dose, route of administration (e.g., oral versus inhaled), and individual susceptibility.

Based on reports that FDA has received, the risk of adverse events from ephedrine can occur at any dosage and may increase when taking a higher dose or taking more frequent doses than at the recommended dosing interval. Therefore, FDA proposes to revise product labeling to inform consumers that use of an OTC bronchodilator drug product can cause an increase in blood pressure and heart rate, which could lead to more serious problems such as heart attack, stroke, and death; and the risks for these problems may increase if the product is taken at higher doses or more frequently than recommended. The labeling also warns consumers against the use of any OTC bronchodilator drug products without a physician's diagnosis of asthma, and directs consumers to consult with a doctor before use, if they have a diagnosis of certain conditions, such as heart disease and high blood pressure.

The proposed labeling for these products has been modified from the labeling in the FM to follow the "Drug Facts" format in § 201.66 (21 CFR 201.66). This standardized format and content for product labeling is intended

to enable consumers to better read and understand the labeling information and to promote the safe and effective use of OTC drug products. The Drug Facts labeling format provides a more structured, organized, and compact presentation of the proposed labeling information for these products. Accordingly, the proposed labeling should help consumers to use these OTC bronchodilator drug products more safely and effectively.

Current labeling in § 341.76(c)(2) states “Do not use this product if you have heart disease, high blood pressure, * * *.” In this proposed rule, FDA is adding the following statements under the heading “When using this product”: “[Bullet] increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack, stroke, and death. Your risk may increase if you take more frequently or more than the recommended dose. [Bullet] * * * rapid heart beat * * * may occur. If these symptoms persist or get worse, consult a doctor right away.”

b. *Warnings related to effects on the nervous system (central and peripheral).* Ephedrine is known to elicit physiological responses similar to catecholamines (i.e., groups of chemically related neurotransmitters, such as epinephrine, norepinephrine, and dopamine). These drugs have stimulant effects on the sympathetic nervous system and thus are classified as sympathomimetic agents (i.e., agents stimulating the sympathetic nervous system (Refs. 12 and 13)). The central effects of ephedrine and epinephrine ingredients include tenseness, nervousness, tremor, and sleeplessness. The peripheral effects primarily include the effects on the cardiovascular system.

The central nervous system effects appear to limit the maximally tolerated dose, which varies widely among individuals as judged by clinical experience

(Ref. 14). Overdose results in exaggeration of the side effects which individuals describe as disagreeable and may help to limit overuse or abuse.

Reported adverse drug events and the known pharmacological data associated with the use of ephedrine and epinephrine ingredients include nervousness, tremor, and seizure. Because of these effects, FDA is proposing to revise product labeling to inform consumers that use of OTC bronchodilator drug products more frequently or at higher doses than recommended may cause adverse effects such as seizure and tremor. Current labeling in § 341.76(c)(5)(ii) states “Some users of this product may experience nervousness; tremor, sleeplessness * * *. If these symptoms persist or get worse, consult your doctor.” In this proposed rule, FDA is placing these warnings under the heading “When using this product” (§ 341.76(c)(4)(ii)) and adding seizure to this warning to read as follows:

“• nervousness, sleeplessness, * * *, tremor, and seizure may occur. If these symptoms persist or get worse, consult a doctor right away.”

FDA is aware that persons with seizure disorders who use ephedrine are at increased risk for experiencing a seizure (Refs. 15, 16, and 17). Epinephrine ingredients have similar pharmacological effects (Refs. 11 and 12). Therefore, in this proposed rule, FDA is amending the warnings to add “seizures” as one of the conditions for which a person should ask a doctor before using OTC bronchodilator drug products.

c. *Warnings related to effects on urination.* Ephedrine and epinephrine ingredients may cause difficulty in urination in males, particularly in older males, who might have an enlarged prostate gland. Current labeling in § 341.76(c)(2) states “Do not use this product if you have * * * difficulty in urination due to enlargement of the prostate gland.” In this proposed rule, FDA

is simplifying this language under the heading “Ask a doctor before use if you have” to read “* * * trouble urinating due to an enlarged prostate gland”.

d. *Warnings related to glaucoma.* Current warnings in the monograph for OTC bronchodilator drug products do not include any information about glaucoma. Glaucoma is a group of diseases that are distinguished by an increase in pressure inside the eye. There are two major types of glaucoma: (1) Chronic or primary open-angle glaucoma and (2) acute closed-angle glaucoma (also known as narrow angle glaucoma). Approximately 90 to 95 percent of people with glaucoma have the open-angle variety, while 5 to 10 percent have closed-angle glaucoma (Ref. 18). Normally, aqueous humor (a clear fluid produced within the eye) drains out of the eye through a drainage site. However, in people with narrow angle glaucoma, sympathomimetic drugs (e.g., ephedrine) cause pupil dilatation (mydriasis) that may result in blockage of the normal drainage site (Refs. 18 through 21). Because the fluid within the eye cannot drain properly in these predisposed individuals, the fluid pressure inside the eyeball increases quickly, leading to the symptoms of narrow angle glaucoma (Ref. 19). Therefore, in this proposed rule, FDA is proposing to add “narrow angle glaucoma” as one of the conditions under the warning subheading “Ask a doctor before use if you have”.

FDA considers it beneficial for consumers to know this information and encourages them to ask their physician in order to be fully informed. FDA has previously included this type of information in the labeling of OTC ophthalmic vasoconstrictor drug products containing topically applied ephedrine (21 CFR 349.75(c)(2)).

e. *Warnings related to nausea and loss of appetite.* Ephedrine may cause nausea and loss of appetite in some people. Current labeling in

§ 341.76(c)(5)(ii) states “Some users of this product may experience * * * nausea and loss of appetite. If these symptoms persist or get worse, consult your doctor.” In this proposed rule, FDA is deleting “nausea” and “loss of appetite” as side effects because they are minor in comparison to other side effects included in product labeling.

f. Warnings related to interactions with drugs used for psychiatric or emotional conditions. Current labeling in § 341.76(c)(4) contains a drug interaction precaution not to use an OTC bronchodilator drug product “if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions * * *).” In this proposed rule, to be consistent with the Drug Facts labeling format in § 201.66, FDA is deleting the words “Drug interaction precaution.” FDA believes that the information about MAOIs in the labeling may be ineffective because some users of OTC bronchodilator drug products may not know that a drug they are taking is an MAOI. In this proposed rule, FDA is including information about the use of prescription drugs for depression or psychiatric or emotional conditions under the subheading “Ask a doctor or pharmacist before use if you are”. Therefore, in this proposed rule, FDA is including an additional warning:

“• Ask a doctor or pharmacist before use if you are taking prescription drugs for * * * depression, or psychiatric or emotional conditions”.

g. Warnings related to interactions with other drugs, foods, and beverages. FDA is aware that certain other drugs, foods, and beverages can interact with OTC ephedrine and epinephrine ingredients and cause an increased stimulant effect. The drugs include other sympathomimetic agents such as pseudoephedrine, phenylephrine, phenylpropanolamine, and caffeine. Some

foods and beverages contain caffeine, and some dietary supplements contain other ingredients reported or claimed to have a stimulant effect.

FDA previously determined that certain combinations of these ingredients presented a potential hazard to health. In the **Federal Register** of August 13, 1982 (47 FR 35344), FDA announced that it had determined that combination drug products consisting of caffeine, phenylpropanolamine, and ephedrine are new drugs and are required to be the subject of an approved new drug application.

A number of sympathomimetic amines have been marketed as prescription drugs used for the treatment of obesity. These include benzphetamine hydrochloride, dextroamphetamine sulfate, diethylpropion hydrochloride, methamphetamine hydrochloride, phendimetrazine tartrate, phentermine hydrochloride and phentermine resin, and sibutramine hydrochloride monohydrate. These sympathomimetic drugs can interact with OTC ephedrine and epinephrine bronchodilator drug products (also sympathomimetics) and cause an increased stimulant effect. Current labeling in § 341.76(c)(3) states "Do not use this product * * * if you are taking any prescription drug for asthma unless directed by a doctor." In this proposed rule, FDA is adding "obesity" and "weight control" to this warning, which now appears under the subheading "Ask a doctor or pharmacist before use if you are," to read as follows:

"• taking prescription drugs for * * * obesity, weight control * * *".

Two studies indicate that the stimulant effects of ephedrine increase when combined with caffeine (Refs. 22 and 23). Caffeine is a nervous system stimulant that can induce nervousness, insomnia, and tachycardia (rapid heart rate) (Refs. 24, 25, and 26). FDA is concerned that taking caffeine and

ephedrine at the same time may increase sympathetic stimulation of the cardiovascular system and nervous system, e.g., increased heart rate, insomnia, and nervousness. In the **Federal Register** of September 27, 2001 (66 FR 49276), FDA issued a final rule establishing that any oral OTC bronchodilator active ingredient in combination with certain pharmacological drug categories, including any stimulant active ingredient, is not generally recognized as safe and effective and is misbranded for OTC use. FDA stated that it did not believe that any such combination drug products are currently marketed OTC.

Although OTC bronchodilator drug products containing ephedrine ingredients in combination with caffeine are not allowed and are not currently marketed, current labeling of OTC ephedrine drug products does not contain a warning about the concurrent use of products containing caffeine or other ingredients that may have a stimulant effect. FDA considers it essential to warn consumers of the risk of excessive use of ephedrine and epinephrine ingredients from any source or use in combination with other products that have stimulant effects. These products include other sympathomimetic drugs, foods or beverages containing caffeine, and dietary supplements containing ingredients reported or claimed to have a stimulant effect.

In this proposed rule, FDA is proposing to add the following warnings to the FM to address concurrent use of different stimulant products:

- Under the subheading “Ask a doctor or pharmacist before use if you are”, the statement “taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)”.

- Under the subheading “When using this product”, the statements “avoid caffeine-containing foods or beverages” and “avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect”.

h. *Other additional warnings.* The FM for OTC bronchodilator drug products contains seven active ingredients (see section I.B of this document). FDA believes that additional warnings are necessary to inform mild asthmatics of the need to carefully follow the warnings and directions for OTC bronchodilator drug products containing any of these active ingredients. FDA is also concerned that possible serious consequences could develop from excessive use of OTC bronchodilator drug products, or continued use of these products by an asthmatic who needs professional medical attention. Therefore, in this proposed rule, FDA is including additional warnings in § 341.76 for OTC bronchodilator drug products.

FDA considers it necessary to inform mild asthmatics that asthma, if not treated appropriately, can worsen and be life-threatening. To emphasize this concern in this proposed rule, FDA is including the following “Asthma alert” warning in § 341.76(c)(5)(i) for ephedrine products:

Asthma alert: Because asthma can be life threatening, see a doctor if you [in bold type]:

- are not better in 60 minutes
- get worse
- need [insert total number of dosage units that equals 150 milligrams] in any day
- use more than [insert total number of dosage units that equals 100 milligrams] a day for more than 3 days a week
- have more than 2 asthma attacks in a week

In this proposed rule, FDA is including the following similar “Asthma alert” warning in § 341.76(c)(6)(i) for epinephrine products for use in a hand-held rubber bulb nebulizer, which states:

Asthma alert: Because asthma can be life threatening, see a doctor if you
[in bold type]

- are not better in 20 minutes
- get worse
- need 12 inhalations in any day
- use more than 9 inhalations a day for more than 3 days a week
- have more than 2 asthma attacks in a week

i. *New labeling format.* In order to make OTC drug product labeling easier to read and understand, and to help ensure the safe and effective use of all OTC drug products, FDA is revising the current labeling in the OTC bronchodilator FM to conform to the standardized OTC drug product labeling format in § 201.66. This labeling format is included in this proposed rule and requires the use of specific language in the labeling of OTC bronchodilator drug products.

3. Directions

FDA is proposing to revise the directions in § 341.76(d)(1) and (d)(2) to include the statement “do not exceed dosage” [in bold type] as the first bulleted statement under the heading “Directions”. This revision is intended to more prominently inform users of these products not to exceed the recommended dosage.

D. Related FDA Regulatory Actions

FDA has exercised its authority under the act to take regulatory action against OTC bronchodilator drug products containing ephedrine ingredients being marketed directly or indirectly for unapproved uses (e.g., stimulant, weight control, and athletic performance enhancement) via a product name that suggested one of these uses. Since the 1995 proposal, FDA issued warning

letters to companies whose products have been linked to significant adverse reactions.

One letter was for a product that contained ephedrine and another ingredient (an expectorant) (Ref. 27). FDA noted that the “statement of identity” and “indications” portion of the product label state the correct uses. However, the trade name of this product suggested it was intended to aid in weight loss, an unapproved use for these ingredients. FDA stated its belief that because there are serious health risks inherent in the promotion of ephedrine for weight loss, the trade name of the product must be changed in order to ensure that the product is not promoted for the unacceptable weight loss use.

FDA stated in another letter that the product’s trade name suggests it is intended for stimulant and recreational use (Ref. 28). FDA had received reports of adverse reactions linked to the use of this product as a stimulant.

FDA requested that these manufacturers take action immediately to correct these violations and stated that failure to do so may result in regulatory action (e.g., seizure and/or injunction). In response to these warning letters, the manufacturers agreed to revise their ephedrine-containing drug product trade names (Refs. 29 and 30).

E. Related DEA Regulatory Actions

In the **Federal Register** of October 11, 1994 (59 FR 51365), DEA issued a final rule eliminating the threshold for single-entity ephedrine drug products. The threshold is an amount of a listed chemical that determines if a transaction such as receipt or sale of the chemical is a regulated transaction under 21 CFR part 1310. The final rule subjected all transactions involving bulk ephedrine and single-entity ephedrine drug products, regardless of size, to the requirements for regulated transactions for listed chemicals under the

applicable provisions of the Controlled Substances Act (see 21 U.S.C. 802(39)(A)), which includes recordkeeping, reporting, and notification.

DEA regulations require that in retail settings open to the public where single-entity ephedrine products are sold, such drugs must be stocked behind a counter where only employees have access (21 CFR 1309.71(a)(2)). In addition, each person who sells these products must identify the other party to the transaction by having the other party present documents that would verify the identity (i.e., a driver's license and one other form of identification) and address of the other party (21 CFR 1310.06 and 1310.07(d)). The required recordkeeping includes the date of the transaction, quantity, form of packaging of the ephedrine product, method of transfer (company truck, picked up by customer, etc.), and type of identification used by the purchaser to the regulated person at the time the order is placed (21 CFR 1310.06).

IV. FDA's Tentative Conclusions

A. Summary of Major Labeling Changes

Over the past 28 years since the Panel report was published, updated guidelines for the treatment of asthma have been issued, e.g., "Guidelines for the Diagnosis and Management of Asthma" (Ref. 5). The benefits of bronchodilator drug products containing ephedrine or epinephrine as a treatment for mild bronchospasms continue to outweigh their risks. FDA recognizes that some people with asthma have used such products intermittently for many years and obtain a benefit from continued availability. FDA is proposing to update the labeling for these products to provide for safer and more effective use. Based on the available evidence, FDA is proposing to amend the FM for OTC bronchodilator drug products to make the changes set

forth in the following paragraphs (sections IV.A.1 through IV.A.3 of this document).

1. Indications

FDA is proposing to revise the indications in § 341.76(b)(1) and (b)(2) to a single indication in the new OTC drug labeling format.

2. Warnings

FDA is proposing to revise the entire warnings section as follows:

- Add an “Asthma alert” section that lists four conditions in which the user of the product should see a doctor. This “Asthma alert” shall appear as the first statement under the heading “Warnings” and parts of the alert shall be in bold type. This new warning replaces the warning previously found in § 341.76(c)(5)(i) for ephedrine ingredients and in § 341.76(c)(6)(ii) for epinephrine ingredients.

- List a number of statements that follow the subheading “Do not use.” These statements include the warnings previously found in § 341.76(c)(1), (c)(4), and (c)(6)(iii), where applicable, for products intended for use in a hand-held rubber bulb nebulizer.

- List a number of conditions for which consumers should consult a doctor before using these products under the subheading “Ask a doctor before use if you have.” This list includes the conditions previously stated in § 341.76(c)(2), plus several additional conditions.

- List a number of other drugs that people might also be taking at the same time and thus should consult a doctor before using the OTC bronchodilator drug product. This information appears under the subheading “Ask a doctor or pharmacist before use if you are.” This list includes prescription drugs for asthma previously stated in § 341.76(c)(3) plus a new list of other drugs that

could cause side effects when used in conjunction with ephedrine or epinephrine ingredients.

• List certain information that consumers need to know under the heading “When using this product.” This information includes the following:

- Side effects that may occur (including side effects currently listed in § 341.76(c)(5)(ii)),
- Information about problems that may occur if the drug is taken more frequently or at a higher than recommended dosage (currently in § 341.76(c)(6)(i) for products containing epinephrine ingredients, and which FDA is now proposing to include for both products containing ephedrine or epinephrine ingredients), and
- New information about avoiding certain foods and dietary supplements while using an OTC bronchodilator drug product.

FDA considers the new information about the risks associated with an increase in blood pressure and heart rate to be the most important of this information and that consumers’ attention should be specifically directed to this information. Accordingly, FDA is proposing that this information appear in bold type as the first statement in this section.

3. Directions

FDA is proposing to revise the directions in § 341.76(d)(1) and (d)(2) to include the statement “do not exceed dosage” [in bold type] as the first bulleted statement under the heading “Directions”.

B. Statement About Warnings

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA’s

requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (see § 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see the final rule on Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use (67 FR 72555, December 6, 2002).

V. Proposed Implementation

FDA proposes that the requirements of a final rule based on this proposed rule be effective within 6 months after publication in the **Federal Register** to provide for safe and effective use of OTC bronchodilator drug products at the earliest possible time because of the safety issues involved with the use of OTC bronchodilator drug products. Therefore, on or after 6 months after the date of publication in the **Federal Register** of a final rule based on this proposed rule, any OTC bronchodilator drug product that is subject to the final rule and that contains nonmonograph labeling or packaging may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Any OTC bronchodilator

drug product that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of a final rule, and is not in compliance with the regulations, is subject to regulatory action. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce cannot be repackaged or relabeled with the prior monograph labeling for these products after the effective date of a final rule based on this proposed rule. Manufacturers are encouraged to comply voluntarily with this proposed rule at the earliest possible date.

VI. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.”

The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. OMB has determined this rule is a significant regulatory action under the Executive order. The purpose of this proposed rule is to revise and improve the labeling (add additional warning statements, change the directions, and change the format for the indications) for OTC bronchodilator drug products. The revised labeling is intended to provide consumers more and better information to help ensure the safe and effective use of all OTC bronchodilator drug products that contain these ingredients. This proposed rule amends the FM for OTC bronchodilator drug products and requires relabeling of all products covered by the FM. Potential benefits include safer use of these products by consumers.

FDA's Drug Listing System (DLS) identifies approximately 25 manufacturers/distributors of approximately 40 to 50 OTC bronchodilator drug products. Approximately half of the manufacturers/distributors market single-ingredient ephedrine drug products, and the other half market combination ephedrine/guaifenesin drug products. There appears to be a very limited number of manufacturers/distributors marketing OTC epinephrine solution products. There may be some additional marketers and combination products sold via magazines and the Internet, which are not in the DLS.

A. Relabeling Costs

FDA believes that the proposed relabeling costs of the type set forth in this document generally average about \$3,000 to \$4,000 per stock keeping unit

(SKU) (individual products, packages, and sizes). Assuming that there are about 50 affected OTC drug products in the marketplace, total one-time costs of relabeling would be \$150,000 (\$3,000 per SKU x 50 SKUs) to \$200,000 (\$4,000 per SKU x 50 SKUs). Even if there are 20 additional products that FDA is not aware of, total one-time costs of relabeling should not exceed \$280,000 (\$4,000 per SKU x 70 SKUs). FDA believes that actual costs would be lower for several reasons. First, it is FDA's understanding that most of the label changes will be made by private label manufacturers that tend to use relatively simple and less expensive labeling. Second, FDA has revised the labeling format in this proposed rule based on the OTC drug product labeling format in § 201.66. Therefore, manufacturers will not incur expenses determining how to state the new information in product labeling. Manufacturers, however, may incur some expense to redesign product labeling.

Most of the manufacturers who produce affected products are small entities, using the U.S. Small Business Administration designations for this industry (750 employees). FDA believes that any other unidentified manufacturer of these products is also a small entity. Those manufacturers who must relabel a large number of their products or manufacture a new smaller size package will incur the greatest economic impact.

B. Regulatory Alternatives Considered

Although FDA has rejected this alternative, FDA had proposed in 1995 to amend the FM for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify those ingredients as not generally recognized as safe and effective for OTC use. In this proposed rulemaking, FDA considered but rejected several other labeling and packaging alternatives: (1)

A longer implementation period, (2) an exemption from coverage for small entities, and (3) less labeling information. FDA does not consider these alternatives acceptable because they do not assure that consumers will have the most recent needed information for safe and effective use of these OTC bronchodilator drug products in a timely manner.

This proposed rule does not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed.

There is one other Federal rule that overlaps, but does not conflict with, this proposed rule. DEA regulations (discussed in section III.E of this document) control the distribution of single-entity OTC ephedrine drug products.

This analysis shows that this proposed rule is not economically significant under Executive Order 12866 and that FDA has analyzed regulatory options that would minimize any significant impact of the proposed rule on small entities. Nevertheless, some small entities, especially those private label manufacturers that provide a number of the affected products, may incur significant impacts. Thus, this economic analysis, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VII. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are a "public disclosure of information originally supplied

by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VIII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

X. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposed rule and the agency’s economic impact determination. Submit a single copy of electronic comments or three paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XI. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposed rule be effective 6 months after its date of publication in the **Federal Register**.

XII. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1995N-0205, unless otherwise indicated, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*, 10th ed., edited by J.G. Hardman and L.E. Limbird, McGraw-Hill Co., New York, NY, p. 237, 2001.
2. Chua, S.S. and S.I. Benrimoj, "Non-Prescription Sympathomimetic Agents and Hypertension," *Medical Toxicology*, 3:387-417, 1988.
3. Morgan, P., "The Role of Vasopressors in the Management of Hypotension Induced by Spinal and Epidural Anesthesia," *Canadian Journal of Anesthesiology*, 41(5 Pt 1):404-413, 1994.
4. Boozer, C.N. et al., "Herbal Ephedra/Caffeine for Weight Loss; A 6-Month Randomized Safety and Efficacy Trial," *International Journal of Obesity and Related Metabolic Disorders*, 26:593-604, 2002.
5. "Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program (NAEPP) Expert Panel Report," *National Institutes of Health Publication*, Update on Selected Topics 2002, pp. 3-125, 2002.
6. Naureckas, E.T., and J. Solway, "Mild Asthma," *The New England Journal of Medicine*, 345(17):1257-1262, 2002.
7. The United States Pharmacopeia 28/The National Formulary 23, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 736, 2004.

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List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 341 be amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 341.76 is amended by revising paragraphs (b), (c), and (d) to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

* * * * *

(b) *Indication.* The labeling of the product states the following under the heading “Use”: “for temporary relief of occasional symptoms of mild asthma: [bullet]¹ wheezing [bullet] tightness of chest [bullet] shortness of breath”. Other truthful and nonmisleading statements, describing only the indication for use that has been established and listed in this paragraph, may also be used as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

¹ See § 201.66(b)(4) of this chapter for the definition of “bullet.”

(c) *Warnings.* The labeling of the product contains the following warnings under the heading “Warnings”:

(1) The following statements shall appear after the subheading “Do not use” [in bold type]:

(i) “[Bullet] unless a doctor said you have asthma”.

(ii) “[Bullet] if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson’s disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.”

(2) The following information shall appear after the subheading “Ask a doctor before use if you have” [in bold type] “[bullet] ever been hospitalized for asthma [bullet] heart disease [bullet] high blood pressure [bullet] diabetes [bullet] thyroid disease [bullet] seizures [bullet] narrow angle glaucoma [bullet] a psychiatric or emotional condition [bullet] trouble urinating due to an enlarged prostate gland”.

(3) The following information shall appear after the subheading “Ask a doctor or pharmacist before use if you are” [in bold type]:

(i) “[Bullet] taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions”.

(ii) “[Bullet] taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)”.

(4) The following information shall appear after the subheading “When using this product” [in bold type]:

(i) “[Bullet] increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack, stroke, and death. Your

risk may increase if you take more frequently or more than the recommended dose.” [statements shall appear in bold type as the first statements under this subheading]

(ii) “[Bullet] nervousness, sleeplessness, rapid heart beat, tremor, and seizure may occur. If these symptoms persist or get worse, consult a doctor right away.”

(iii) “[Bullet] avoid caffeine-containing foods or beverages”.

(iv) “[Bullet] avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect”.

(5) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16(a), (b), (c), and (f).*—(i) The following information shall appear after the subheading “Asthma alert: Because asthma can be life threatening, see a doctor if you” [in bold type]:

(A) “[Bullet] are not better in 60 minutes”.

(B) “[Bullet] get worse”.

(C) “[Bullet] need [insert total number of dosage units that equals 150 milligrams] in any day”.

(D) “[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] a day for more than 3 days a week”.

(E) “[Bullet] have more than 2 asthma attacks in a week.”

(ii) This “Asthma alert” shall appear on any labeling that contains warnings and shall be the first warning statement under the heading “Warnings”.

(6) *For products containing epinephrine, epinephrine bitartrate, or racepinephrine hydrochloride identified in § 341.16(d), (e), and (g).*—(i) The

following information shall appear after the subheading “Asthma alert:

Because asthma can be life threatening, see a doctor if you” [in bold type]:

(A) “[Bullet] are not better in 20 minutes”.

(B) “[Bullet] get worse”.

(C) “[Bullet] need 12 inhalations in any day”.

(D) “[Bullet] use more than 9 inhalations a day for more than 3 days a week”.

(E) “[Bullet] have more than 2 asthma attacks in a week.”

(ii) This “Asthma alert” shall appear on any labeling that contains warnings and shall be the first warning statement under the heading “Warnings”.

(iii) *For products intended for use in a hand-held rubber bulb nebulizer.* The following statement shall also appear after the subheading “Do not use” along with the other information in paragraph (c)(1) of this section: “[bullet] if product is brown in color or cloudy”.

(d) *Directions.* The labeling of the product contains the following information under the heading “Directions”:

(1) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16(a), (b), (c), and (f).*—(i) “[Bullet] do not exceed dosage” [sentence appears as first bulleted statement under “Directions” and in bold type].

(ii) “[Bullet] adults and children 12 years of age and over: oral dose is 12.5 to 25 milligrams every 4 hours as needed, not to exceed 150 milligrams in 24 hours”.

(iii) “[Bullet] children under 12 years of age: ask a doctor”.

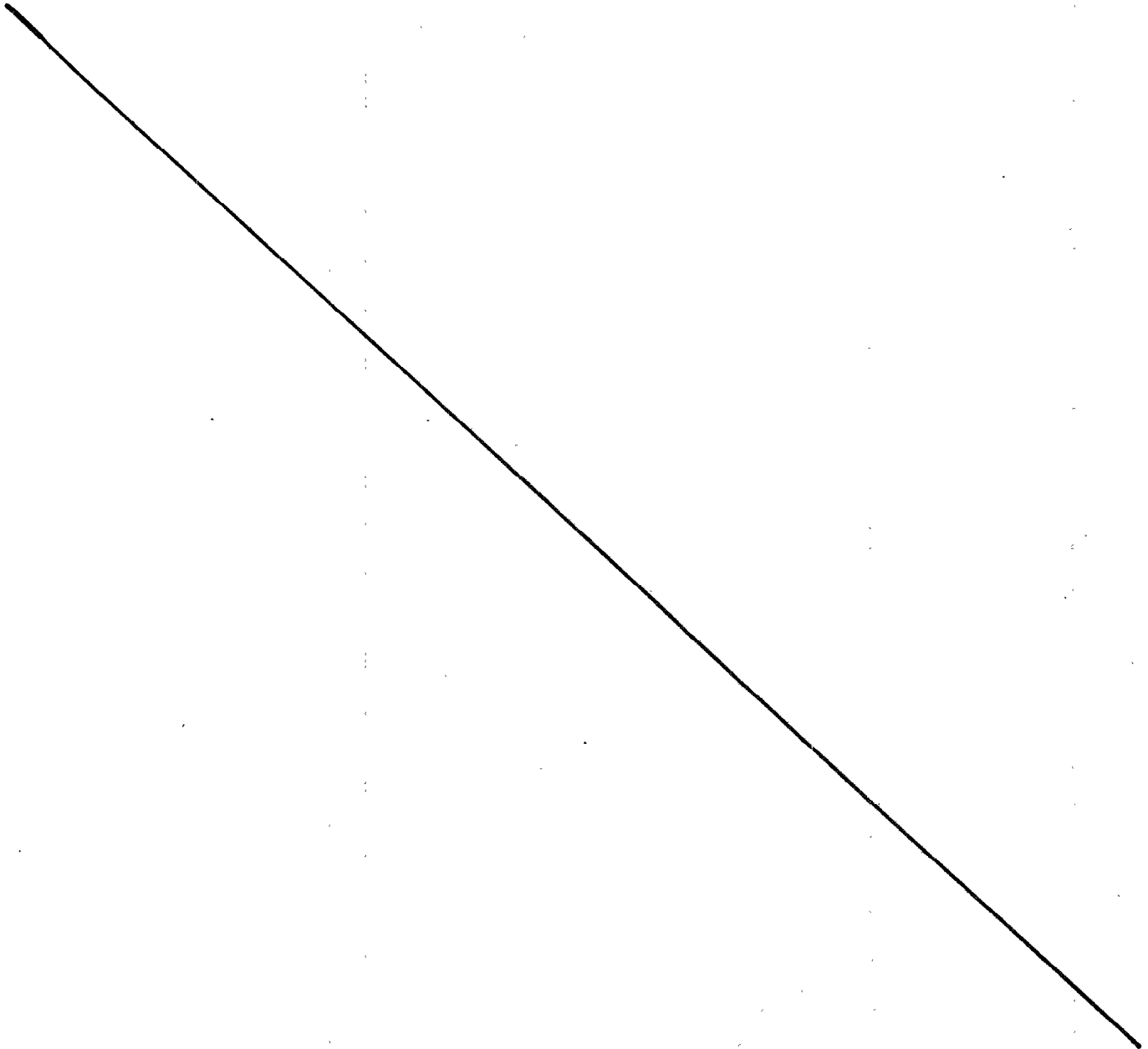
(2) *For products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride identified in § 341.16(d), (e), and (g) for use in*

a hand-held rubber bulb nebulizer. The ingredient is used in an aqueous solution at a concentration equivalent to 1 percent epinephrine.

(i) “[Bullet] do not exceed dosage” [appears as first bulleted statement under “Directions” and in bold type].

(ii) “[Bullet] adults and children 4 years of age and over: 1 to 3 inhalations not more often than every 3 hours. The use of this product by children should be supervised by an adult.”


(iii) “[Bullet] children under 4 years of age: ask a doctor”.



Dated:

June 30, 2005.

6/30/05


Jeffrey Shuren,
Assistant Commissioner for Policy.

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